IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of **Franz-Josef RUBRODER et al.**

Examiner: **Chandra, Gyan**

Application No.: **10/796,160**

Art Unit: **1646**

Filed: **March 10, 2004**

Title: **PROCESS FOR STABILIZATION OF PROTEINS IN COMPLEX MIXTURES DURING THEIE STORAGE IN AQUEOUS SOLVENTS**

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. §41.37

Further to the Notice of Appeal dated October 4, 2007, the following statements in support of the Appeal are submitted as detailed below.

The requisite fee set forth in 37 C.F.R. §41.20(b)(2) and a petition for an extension of time of five months pursuant to 37 C.F.R. §1.136(a) were submitted March 10, 2008; the Appeal Brief is now due April 5, 2008.

APPELLANTS' BRIEF

(1) Real Party in Interest

The real party in interest is SANOFI-AVENTIS DEUTSCHLAND GMBH, (formerly AVENTIS PHARMA DEUTSCHLAND GMBH).

(2) Related Appeals and Interferences

None.

(3) Status of Claims

Claims 23-69 are pending. Claims 23-69 were rejected based on non-statutory obviousness-type double patenting. Claims 23-69 are being appealed. All amendments filed have been entered.

(4) Status of Amendments

None.

(5) Summary of Claimed Subject Matter

Independent claims 23 and 43 claim:

A process for the storage of a protein in an aqueous solution, comprising adding an amount of cysteine effective to delay the temporal decrease in the effective concentration of the protein by reducing chemical modification of SH groups on the protein during storage, wherein the effective concentration does not decrease by more than about 7%. [Claim 23].

A process far the storage of a protein in an aqueous solution, comprising adding an amount of cysteine effective to delay the temporal decrease in the effective concentration of the protein by reducing chemical modification of SH groups on the protein during a period of greater than 24 hours. [Claim 43].

All rejected claims stand or fall together on the utility issue and the enablement issue as it is based on the utility rejection.

(6) Grounds of Rejection for Review on Appeal

The issue for review on appeal is:

A) Claims 23-69 were rejected in a March 7, 2007 final rejection based on non-statutory obviousness-type double patenting.

(7) **Argument**

A) **The obviousness type double patenting rejection of claims 23-69 should be withdrawn at least in accordance with the Terminal Disclaimer filed March 10, 2008.**

The evidence appendix includes a single document, a Terminal Disclaimer filed March 10, 2008. This filing should suffice to remove any reasons for rejection of claims 23-69.

In view of this evidence, the Board is respectfully requested to review and reverse the present obviousness-type double patenting rejection.

The Commissioner is hereby authorized to charge any additional fees or credit any overpayment resulting from this submission to Deposit Account 18-1982.

Respectfully submitted,

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(8) Claims Appendix

The appealed claims are:

23. A process for the storage of a protein in an aqueous solution, comprising adding an amount of cysteine effective to delay the temporal decrease in the effective concentration of the protein by reducing chemical modification of SH groups on the protein during storage, wherein the effective concentration does not decrease by more than about 7%.

24. The process as claimed in claim 23, wherein the effective concentration does not decrease by more than about 3%.

25. The process as claimed in claim 23, wherein the protein is a heterologous protein produced in an organism.

26. The process as claimed in claim 68, wherein the microorganism is a bacterium.

27. The process as claimed in 26, wherein the bacterium is *Escherichia coli.*

28. The process as claimed in claim 68, wherein the microorganism is a yeast.

29. The process as claimed in claim 28, wherein the yeast is *Saccharomyces cerevisiae.*

30. The process as claimed in claim 28, wherein the yeast is *Pichia pastoris.*

31. The process as claimed in claim 23, wherein the protein is a heterologous protein and is produced in an insect cell.

32. The process as claimed in claim 25 or claim 31, wherein the protein is encoded by an expression vector.

33. The process as claimed in claim 23, wherein the protein is present in dissolved form.

34. The process as claimed in claim 23, wherein the protein is present in suspension.

35. The process as claimed in claim 23, wherein the storage of the protein takes place at about 0°C to about 50°C.

36. The process as claimed in claim 35, wherein the storage of the protein takes place at about 5°C to about 30°C.

37. The process as claimed in claim 35, wherein the storage of the protein takes place at about 5°C.

38. The process as claimed in claim 23, wherein the protein is insulin, an insulin derivative, or a precursor thereof.

39. A process for the preparation and storage of a heterologous protein, comprising the expression of the heterologous protein or a precursor thereof in a transformed microorganism, optional disruption of the microorganism and/or isolation of the heterologous protein or its precursor from the culture medium, and the subsequent storage of the heterologous protein according to the process of claim 23.

40. The process of claim 39, further comprising the renaturation of the heterologous protein or its precursor and the purification of the heterologous protein, including optional removal of a leader sequence or other sequences that may be present in the precursor of the heterologous protein.

41. The process as claimed in claim 39, wherein the heterologous protein is animal insulin.

42. The process as claimed in claim 41, wherein the animal insulin is human insulin.

43. A process far the storage of a protein in an aqueous solution, comprising adding an amount of cysteine effective to delay the temporal decrease in the effective concentration of the protein by reducing chemical modification of SH groups on the protein during a period of greater than 24 hours.

44. The process as claimed in claim 43, wherein the temporal decrease in the effective concentration of the protein is delayed for a period of 48 hours or more.

45. The process as claimed in claim 43, wherein the temporal decrease in the effective concentration of the protein is delayed for a period of 1 week or more.

46. The process as claimed in claim 43, wherein the temporal decrease in the effective concentration of the protein is delayed for a period of 2 weeks or more.

47. The process as claimed in claim 43, wherein the temporal decrease in the effective concentration of the protein is delayed for a period of 4 weeks or more.

48. The process as claimed in claim 43, wherein the temporal decrease in the effective concentration of the protein is delayed for a period of 8 weeks or more.

49. The process as claimed in claim 43, wherein the temporal decrease in the effective concentration of the protein is delayed for a period of from greater than 24 hours to 2 months.

50. The process as claimed in claim 43, wherein the protein is a heterologous protein produced in an organism.

51. The process as claimed in claim 69, wherein the microorganism is a bacterium.

52. The process as claimed in claim 51, wherein the bacterium is *Escherichia coli.*

53. The process as claimed in claim 69, wherein the microorganism is a yeast.

54. The process as claimed in claim 53, wherein the yeast is Saccharomyces cerevisiae.

55. The process as claimed in claim 53, wherein the yeast is *Pichia pastoris.*

56. The process as claimed in claim 43, wherein the protein is a heterologous protein and is produced in an insect cell.

57. The process as claimed in claim 50 or claim 56, wherein the protein is encoded by an expression vector.

58. The process as claimed in claim 43, wherein the protein is present in dissolved form.

59. The process as claimed in claim 43, wherein the protein is present in suspension.

60. The process as claimed in claim 43, wherein the storage of the protein takes place at about 0°C to about 50°C.

61. The process as claimed in claim 60, wherein the storage of the protein takes place at about 5°C to about 30°C.

62. The process as claimed in claim 60, wherein the storage of the protein takes place at about 5°C.

63. The process as claimed in claim 43, wherein the protein stored is insulin, an insulin derivative, or a precursor thereof.

64. A process for the preparation and storage of a heterologous protein, comprising the expression of the heterologous protein or its precursor in a transformed microorganism, optional disruption of the microorganism and/or isolation of the heterologous protein or its precursor from the culture medium, and the subsequent storage of the heterologous protein according to the process of claim 43.

65. The process of claim 64, further comprising the renaturation of the heterologous protein or its precursor and the purification of the heterologous protein, including optional removal of a leader sequence or other sequences that may be present in the precursor of the heterologous protein.

66. The process as claimed in claim 64, wherein the heterologous protein is animal insulin.

67. The process as claimed in claim 64, wherein the animal insulin is human insulin.

68. The process as claimed in claim 25, wherein the organism is a microorganism.

69. The process as claimed in claim 50, wherein the organism is a microorganism.

(9) Evidence Appendix

A copy of a Terminal Disclaimer downloaded from the Public Pair Page is attached. The Disclaimer is of record as of March 9, 2008 in Transaction History and March 10 in the IFW. The Transaction History indicates "Paralegal TD Accepted" March 18, 2008.

(10) Related Proceedings Appendix

None.